REMARKS

Claims 1, 5-9, 11-15, 20-25, 27 and 29-61 are being examined and all stand rejected.

Information Disclosure Statement

Applicant submitted a Supplemental Disclosure Statement on 14 March 2003 containing references recently received from the European Patent Office as part of the International Search Report for the PCT application corresponding to the parent application (now U.S. Patent 6,323,009) of the present case.

Rejection Under 35 U.S.C. §112, ¶2

All claims have been rejected under section 112, second paragraph, as being indefinite.

Claim 1 was rejected for alleged failure to define the terms "naturally occurring dNTP different from the foregoing" or "dNTP analog" or "dNTP having a universal base." In response, Applicants have amended claim 1 to delete these terms.

Claim 39 was rejected as indefinite for use of the term "target DNA" without antecedent basis. In response, claim 39 has been amended to delete this language.

Claim 50 was rejected for insufficient basis for the term "said 3'-terminal nucleotide" and "said primer." In response, claim 50 has been amended to recite "the 3'-terminal nucleotide" and "the primer." Applicants also note that claim 50 depends indirectly from

claim 1, which does recite a primer and which primer has a 3'-terminus in order to facilitate extension during the amplification process.

Claim 54 was rejected as indefinite for use of the phrase "said target DNA" in line 3 thereof, for which there is contended to be insufficient antecedent basis. In response, claim 54 was amended to remove this language.

Claims 56 and 61 were rejected as indefinite for use of the phrase "such as." In response, Applicants have previously amended claim 56 to remove this language (see previous amendment, filed 27 September 2002).

Claim 60 was rejected as indefinite for use of the phrase "a linear target." In response, claim 60 has been cancelled.

Rejection Under 35 U.S.C. §103

Claims 1, 5-7, 11-14, 20-25, 27, 29, 31, 33, 35-40, 42, 44, 45, 48-54, and 60, 62 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Pat. No. 5,854,033 – Lizardi-1) and Lizardi (U.S. Pat. No. 6,124,120 - Lizardi-2).

In response, Applicant previously amended claim 1 (from which the other claims depend either directly or indirectly) to recite use of dNTPs that render the resulting TS-DNA product resistant to exonucleases. This is not taught or suggested by either of the Lizardi references and thus they do not render the remaining claims unpatentable.

In addition, the Office Action concedes that Lizardi-1 does not teach use of random primers but offers Lizardi-2 to teach random primers with whole genomic DNA. Applicants believe that such combination is inapposite. Lizardi-1 teaches the use of amplification

target circles (ATCs) with a primer to achieve rolling circle amplification (RCA) but does not teach use of multiple primers with an ATC. Rather, Lizardi-1 teaches use of secondary and tertiary primers with additional rounds of RCA (where the templates are not circular (and cannot be circular) because they are the tandem sequence DNA product (or ribbon) that is produced by the RCA process. Conversely, Applicants' claim 1 recites use of multiple primers with a single ATC to amplify the target DNA (in this case, it is the primer sequences that are amplified by being replicated around the ATC, which acts as template) thereby producing a ribbon (or TS-DNA) product comprising tandem sequences of the amplified oligonucleotide segments.

In addition, the only example provided by Lizardi-1 as the source for an ATC is in Figure 1, where it is produced by binding an open circle probe to a target sequence and then ligating. Ligation is not a part of the method of claim 1 of the present application.

One advantage of the present invention over Lizardi is the absence of a ligation step.

The way Lizardi-1 works is that one wants to detect the presence of a target sequence so they contact the DNA to be tested using an open circle probe with 5' and 3' end sequences complementary to separate portions of the oligonucleotide segment to be detected, allow it to hybridize, ligate the ends of the probe to form the ATC, contact with a primer complementary to the ATC and amplify the ATC to form TS-DNA, with secondary and tertiary primers attaching to the TS-DNA to give additional amplification. The presence of the amplified ATC sequences then indicates the presence of the original target sequence to which the ATC bound at the outset.

In the present application, the multiple primers bind to the ATC itself and it acts as a template for amplifying the primer sequences.

Lizardi-2 achieves multiple strand displacement amplification but not on a circular DNA (or ATC). In fact, the office action points to Lizardi-2 at column 2, lines 25-53, but this recites a method in which right and left hand sets of primers are used to attach to a duplex DNA and wherein each such set of primers is complementary to a different strand of the duplex target (column 2, lines 36-39) and each such primer is distal to the sequence to be amplified (column 2, lines 39-43). This is totally different from Applicants' invention, which uses multiple primers on a given ATC (as made clearer by the amendment to claim 1). Thus, Lizardi-2 does not recite methods relevant to Applicants' invention.

Now, as to combining Lizardi-1 and Lizardi-2 in order to achieve Applicants' invention, the office action indicates that the motivation to combine them is found in the desire to amplify unknown DNA sequences with random primers and using double-stranded DNA targets broadens the range of amplifiable target DNAs. (see office action at page 6, first paragraph)

Applicants respond that, while such might be a motivation to combine the two Lizardi patents to achieve such a result, it is not technologically feasible to combine the Lizardi patents in this manner and thus motivation is irrelevant. Lizardi-1 employs an open circle probe to locate a target DNA sequence and then ligates the probe to form an ATC, which ATC is then contacted with a primer for subsequent amplification. Conversely, Lizardi-2 employs a set of primers to bind to duplex (presumably denatured duplex) DNA and amplify each of the strands. Because the template of Lizardi-2 is duplex, possibly linear, it is not an amplification target circle within the meaning of Lizardi-1 and those skilled in the art, while possibly motivated to amplify unknown DNAs, would not be motivated to apply a method using duplex DNA templates in a procedure that employs single stranded amplification target circles formed by hybridization of probes to a target DNA.

In Lizardi-1 the target binds the probe, which is then ligated to form the circle (see Figures 1 to 5 of Lizardi-1). The circle is contacted with a primer and then secondary and

tertiary probes are used to amplify the tandem sequence RCA product. Lizardi-2 uses multiple primers for a duplex target DNA and not on an amplification target circle. In effect, Lizardi-2 is doing the same kind of process as Lizardi-1 in that Lizardi-2 uses multiple primers for each strand of a duplex target while Lizardi-1 is using multiple primers on the single stranded TS-DNA product of RCA. However, neither reference (either alone or in combination) uses multiple primers on an ATC itself and neither suggests doing so.

For example, if one looks at Figure 1 of Lizardi-2, the duplex sequence to be amplified is shown at the top as a cross-hatched area. The primers are all distal to this and therefor each primer must hybridize to a different DNA sequence and one that does not include the target sequence to be amplified. Thus, as each primer extension crosses the target sequence, said sequence will be replicated and thereby amplified. As the process proceeds, other primers not yet bound to the target duplex DNA are free to bind to the single stranded product of the primary replication process and thereby provide additional amplification. In this way, amplification relies on the binding of multiple secondary and tertiary (perhaps even quaternary) primers for additional amplification (see Lizardi-2 at Figures 2, 3 and 4), just as was used in Lizardi-1 (see Lizardi-1 at Figures 1 and 13) but the primary amplification step of Lizardi-1 and Lizardi-2 is sufficiently different that those skilled in the art would not think to combine them. Thus, the method taught in Lizardi-2 is like the secondary and tertiary amplification steps of Lizardi-1 but wholly unrelated (and not usable with) the primary amplification step of Lizardi-1 (where the ATC is used as a template for RCA) and thus those skilled in the art would not be either motivated or able to combine them.

Claims 8 and 9 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Pat. No. 5,854,033 – Lizardi-1) and Lizardi (U.S. Pat. No. 6,124,120 - Lizardi-2) and further in view of Sorge et al (U.S. Patent 5,599,921).

Claim 15 was rejected under section 103 as unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 12 and 13, on grounds that, although neither teaches a

denaturation step, it is common knowledge to use one. Applicant responds that the amendment to claim 1 renders claim 15, which depends from claim 12 or 13, both of which depend from claim 1, patentable over these references because amended claim 1 is patentable over these references.

Claims 32, 41, 46, 47 and 59 were rejected under section 103 as unpatentable over Lizardi-1 and Lizardi-2 and further in view of Skerra (1992), on grounds that Lizardi-1 teaches use of a polymerase with exonuclease activity while Skerra teaches use of a phosphorothioate nucleotide at the 3'-end of a primer to make them exonuclease resistant. In response, Applicant has amended claim 1 to incorporate use of a dNTP that makes the resulting TS-DNA product resistant to exonuclease activity. Use of exonuclease resistant primers is only recited in dependent claim 38 and claims dependent therefrom. Thus, claims 26 and 28 have been cancelled and their limitations incorporated into amended claim 1. Claim 28, and claims dependent therefrom, specifically recited use of a dNTP of claim 26 that would make the resulting TS-DNA resistant to exonuclease activity. Thus, the above claims should be patentable over these references.

Claims 30, 34 and 43 were rejected under section 103 as unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 1, 26 and 43, and further in view of Cummins et al (1996). Applicants believe that this rejection is an oversight in that these claims were cancelled in a previous amendment of the present application.

Claims 55 and 56 were rejected under section 103 as unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 and further in view of Sorge et al (U.S. Patent No. 5,556,722). In response, Applicant has amended claim 1 from which claims 55 depends (claim 56 depends from claim 55) so that these claims now incorporate the limitations of claim 1 as amended, which limitations are drawn from now cancelled claims 26 and 28, thereby making claim 55 patentable over Lizard-1 in view of Cummins et al, since the latter references do not teach use of a dNTP that renders the TS-DNA product resistant to nucleases.

Applicants further note that the office action has offered the argument that because the limitations of claim 26 were previously rejected as anticipated by Lizardi-1 while the limitation of claim 3 was previously rejected as obvious over the combination of the two Lizardi patents, that the combination of these into claim 1 does not render claim 1 patentable over these references. In response, Applicants note that the prior rejections of claims 3 and 26 were separate rejections and the office action makes no argument that these references are still applicable when the limitations of claims 3 and 26 have both been incorporated into the same claim 1. Thus, whether each limitation might separately not be patentable over a reference does not mean that, when combined, the resulting claim is not patentable, especially where the original ground of rejection of each of the separately claimed limitations was not identical.

Claims 57 and 58 were rejected under section 103 as unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 since these claims are directed to use of a reverse transcriptase with and without RNA. Applicant responds that the amendment of claim 1 to recite use of a dNTP that causes the product to be resistant to nucleases, as well as multiple primers, renders claims 57 and 58 patentable over these references since they in no way suggest such limitations. For example, the fact that compounds A and B are both disclosed in a single reference does make it obvious to react them to form compound C.

Rejection Based on Double Patenting

Claims 1, 5-9, 11-15, 20-25, 27 and 29-61 have been rejected for obviousness-type double patenting based on claims 1-67 of U.S. Patent No. 6,323,009 B1. In response, Applicants submit herewith a Terminal Disclaimer. The cited patent is based on the parent application of the present one and both are assigned to the same assignee.

Applicant has included herewith a Request for a 3 month extension of time to respond and has also included payment for this time period for a small entity plus the required fee for a statutory disclaimer. The Commissioner is authorized to charge payment of any additional fees required under 37 CFR 1.16 associated with this communication or credit any overpayment to Deposit Account No. 03-0678.

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Alan J. Grant 6/12/03
Alan J. Grant, Esq. **Date**

Respectfully submitted,

Alan J. Grant

Alan J. Grant, Esq.
Reg. No. 33,389

CARELLA, BYRNE BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
Six Becker Farm Road
Roseland, NJ 07068
Phone: 973-994-1700
Fax: 973-994-1744